CDER New Drug Review: 2012 Update

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FDA/CMS Summit
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Housekeeping

- Data and analyses presented today are thought to be accurate, but in order to provide the most up-to-date information they have not undergone the same thorough quality control as is performed for official FDA reports
- Analyses of NME/original BLA filings and approvals will be abbreviated to "NME"
- Many staff in CDER provided data, analyses, and PowerPoint expertise for this talk
  - A special acknowledgement to Michael Lanthier, Nelson Cheung, Chintan Shah, and Sally Worrell for their outstanding help in conceiving and conducting many of the analyses. Their behind the scenes work makes me look good.

Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
  - IND activity, NME submissions, and NME approvals
  - Use of expedited pathways
  - Rare diseases
  - Emerging sponsors
- Implementation of PDUFA V/FDASIA
  - "Program" for NME review
  - Enhanced Communication During Drug Development
  - Breakthrough Products

What about PDUFA Goals?

- FDA continues to take PDUFA goals very seriously
  - These are commitments that we make to Congress and the American public for how we will do our work
- FDA is meeting or exceeding nearly all PDUFA goals for application review

CDER Review Performance for FY 2011*

Submission Type	Number Filed	2011 Performance Goal	Current Performance
New Drug Applications / Biologic License Applications*			
Standard	**74**	**90% in 10 months**	**99%**
Priority	**22**	**90% in 6 months**	**95%**
NMEs/New BLAs			
Standard	**18**	**90% in 10 months**	**100%**
Priority	**14**	**90% in 6 months**	**93%**
NDA / BLA Resubmissions			
Class 1	**9**	**90% in 2 months**	**100%**
Class 2	**49**	**90% in 6 months**	**100%**
NDA / BLA Efficacy Supplements			
Standard	**95**	**90% in 10 months**	**95%**
Priority	**23**	**90% in 6 months**	**96%**
NDA / BLA Efficacy Supplement Resubmissions			
Class 1	**11**	**90% in 2 months**	**82%**
Class 2	**21**	**90% in 6 months**	**95%**
NDA / BLA Manufacturing Supplements			
Requiring Prior Approval	**578**	**90% in 4 months**	**94%**
CBE	**1318**	**90% in 6 months**	**97%**

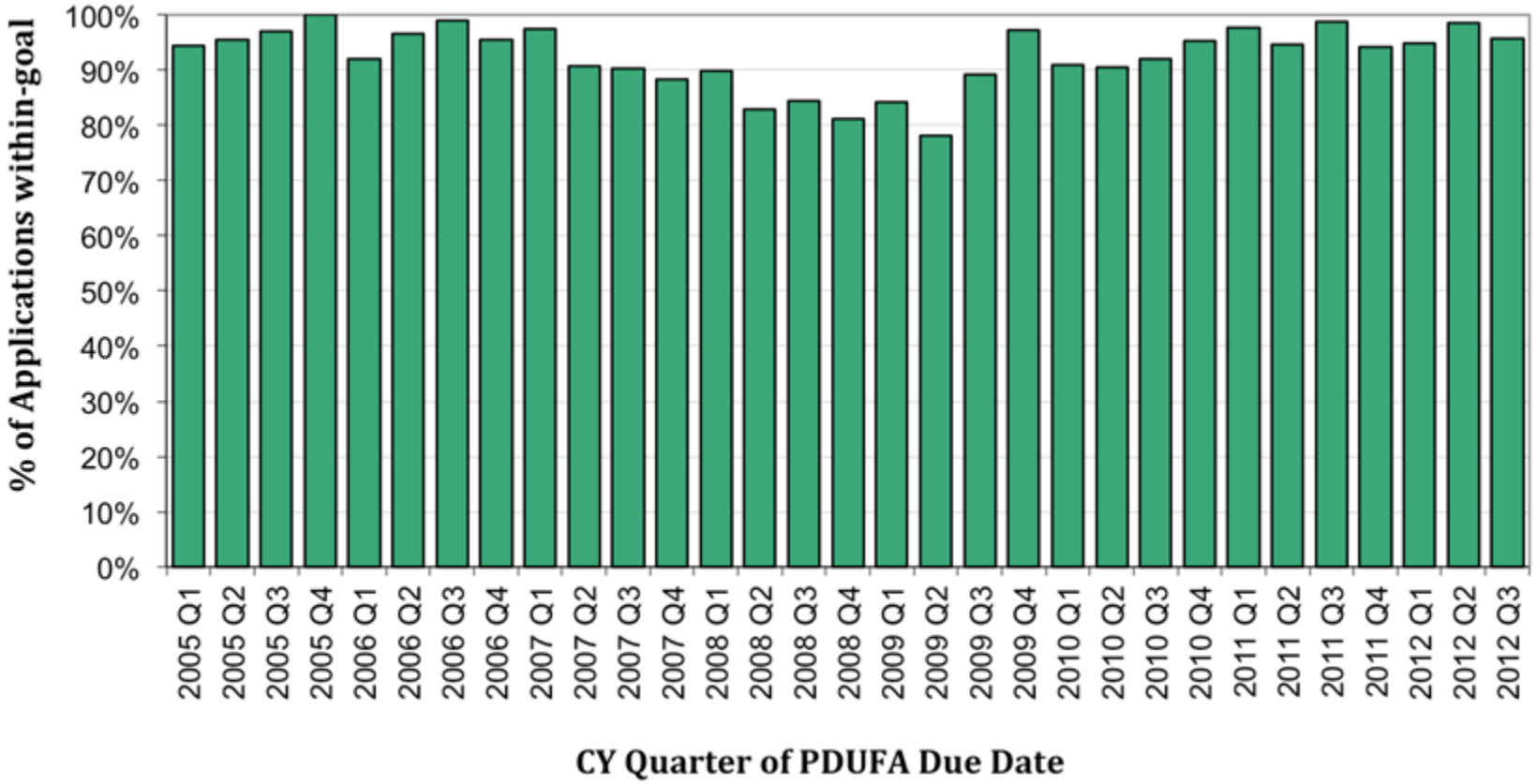
•* Data as of September 30, 2012

CDER Review Performance for FY 2012*

Submission Type	Number Filed**	2012 Performance Goal	Potential Performance % of Actions Within Goal***
*New Drug Applications / Biologic License Applications****			
Standard	96	90% in 10 months	100%
Priority	26	90% in 6 months	96%
NMEs/New BLAs			
Standard	27	90% in 10 months	100%
Priority	16	90% in 6 months	94%
NDA / BLA Resubmissions			
Class 1	7	90% in 2 months	100%
Class 2	32	90% in 6 months	100%
NDA / BLA Efficacy Supplements			
Standard	97	90% in 10 months	100%
Priority	34	90% in 6 months	100%
*Undetermined****	4		
NDA / BLA Efficacy Supplement Resubmissions			
Class 1	2	90% in 2 months	100%
Class 2	14	90% in 6 months	86%
NDA / BLA Manufacturing Supplements			
Requiring Prior Approval	716	90% in 4 months	94%
CBE	1055	90% in 6 months	98%

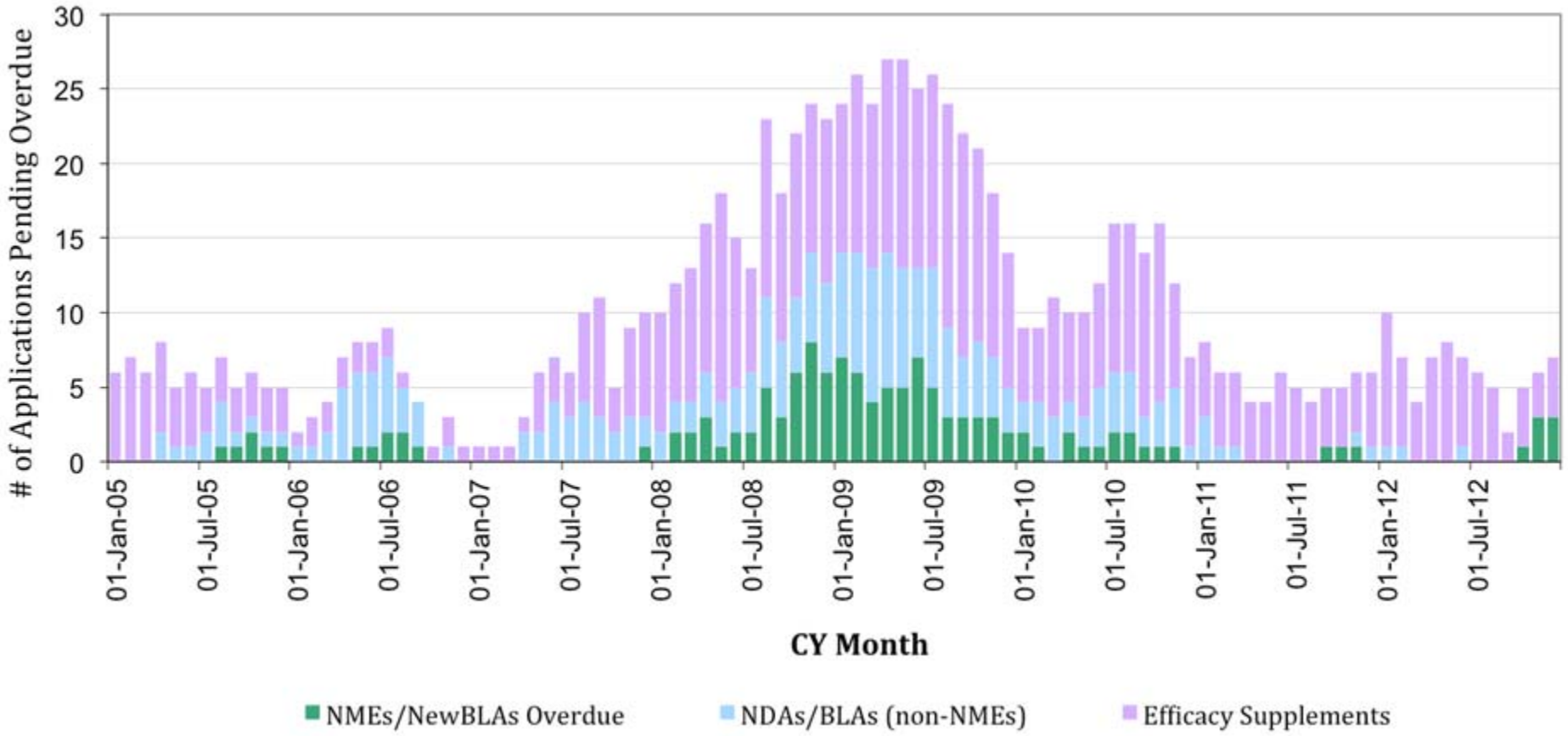
- * Data as of September 30, 2012
- ** Submissions that are pending a filing decision are counted as filed.
- *** *Potential Performance* - level of performance that could potentially be achieved if all the actions currently pending are reviewed within their required goal date.
- **** *Undetermined* - applications that have not had their 60 day filing meeting yet and may not have their review classification determined.

CDER PDUFA Application Review Performance (NDAs, BLAs, Efficacy Supplements)



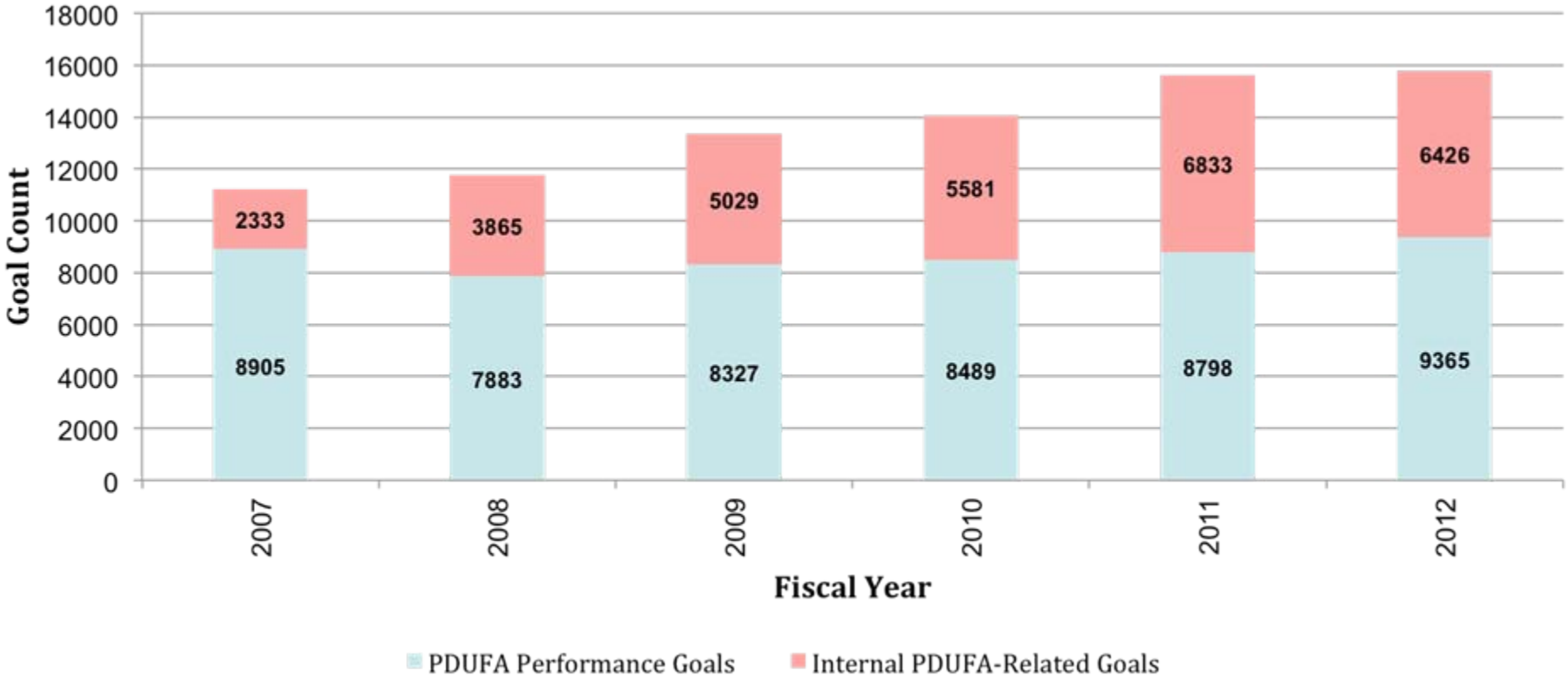
•*CDER data as of 11/30/2012. Figures reflect aggregate performance for all NDAs, BLAs, and Efficacy Supplements based on the month of the PDUFA review goal.

CDER Pending Applications with Overdue PDUFA Goals



•*CDER data as of 11/30/2012. Figures reflect the number of NDAs, BLAs and efficacy supplements that are pending and overdue on their PDUFA goal date, evaluated on the first day of each month.

Behind the scenes: A Growing Mountain of Tracked Goals under PDUFA



- *FY2011 and FY2012 Figures as of September 30, 2012
- Number of tracked goals will increase further under PDUFA V for NME Program, etc.

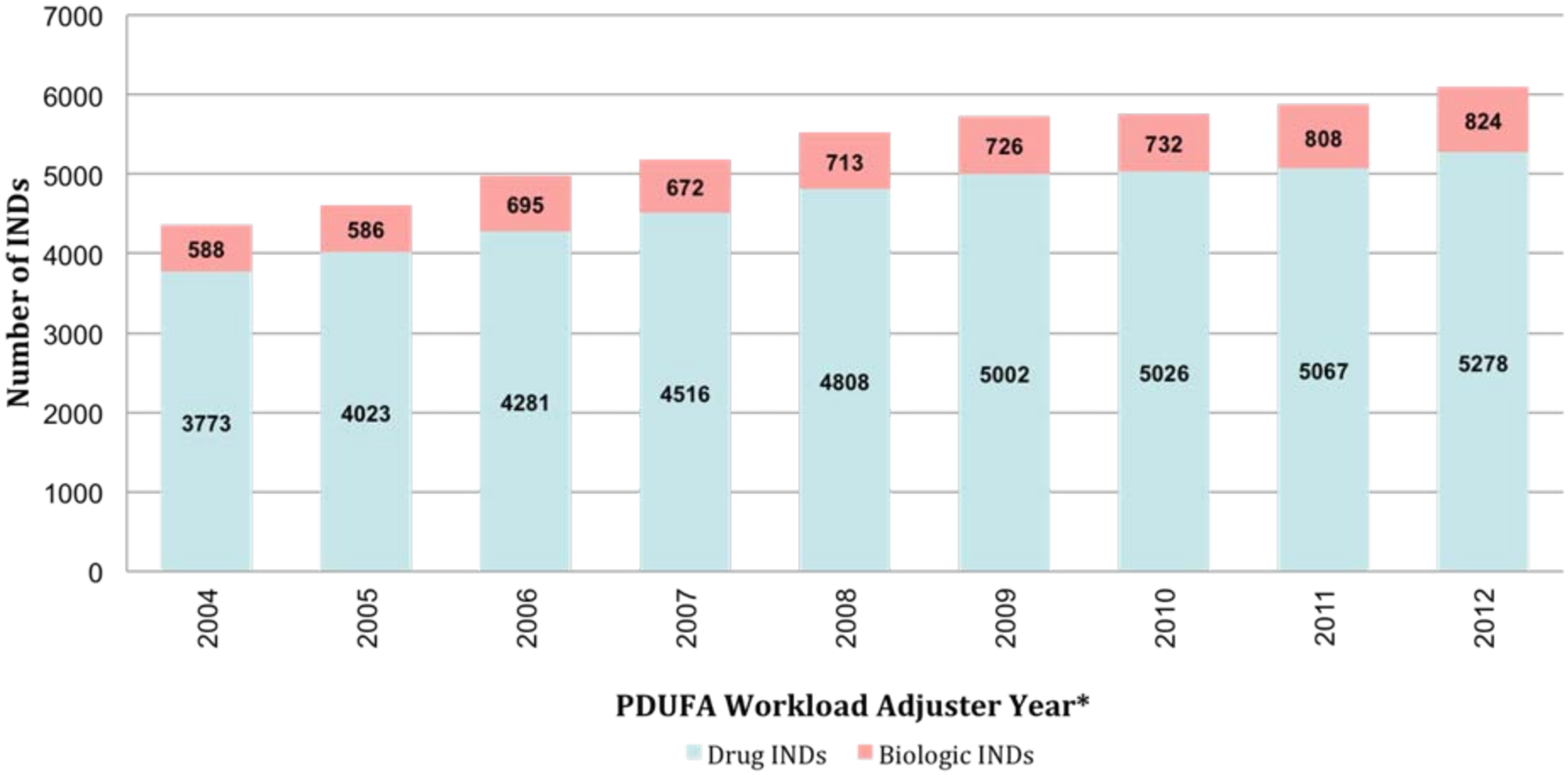
What about new drug approvals?

- The commercial IND pipeline of new drugs under development remains strong and is growing
- Through Nov 30, in CY12 CDER has received 34 NME applications
  - Some are still within the 60-day filing window, subject to RTF
  - A surge of submissions often occurs in December
  - Number of NMEs filed for review is a major rate-limiting step to the number of NMEs approved
- To date in CY12 CDER has approved 31 NME applications
  - CY 12 total to date is one more than the total approved in CY11 and highest total since 2004
  - Several NMEs have PDUFA goal dates before end of December
    - Potential exists for highest number of approvals since mid-90's but it's premature to predict the final total

What about new drug approvals (cont)?

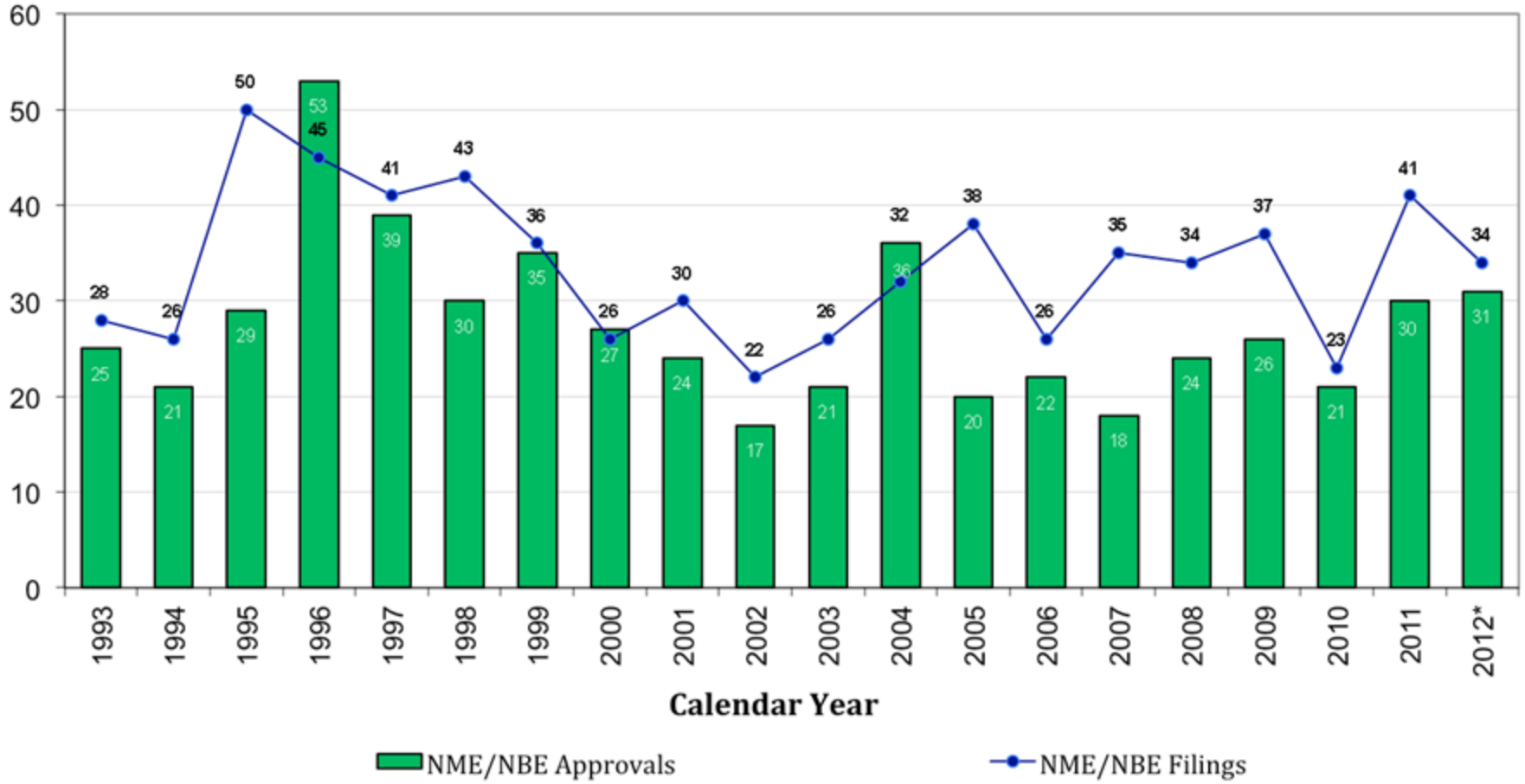
- NME approvals in 2012 include a number of "breakthrough" drugs that provide much needed new treatment options for patients
- Continuing trend in 2012 NME approvals for rare diseases and applications submitted by "emerging" sponsors
- Average first cycle approval rates for NME applications in PDUFA IV are at the highest levels since the start of PDUFA; possible reasons include:
  - Full implementation of 21st Century Review Model
  - Greater experience with use of FDAAA tools (e.g., REMS, PMRs)
  - Targeted therapy with large effect size and increased focus on rare diseases, which improves benefit/risk ratio
  - Fall in "me-too" submissions for chronic symptomatic diseases where benefit/risk ratio is often less favorable

Commercial INDs with Activity Based on PDUFA Workload Adjuster Data



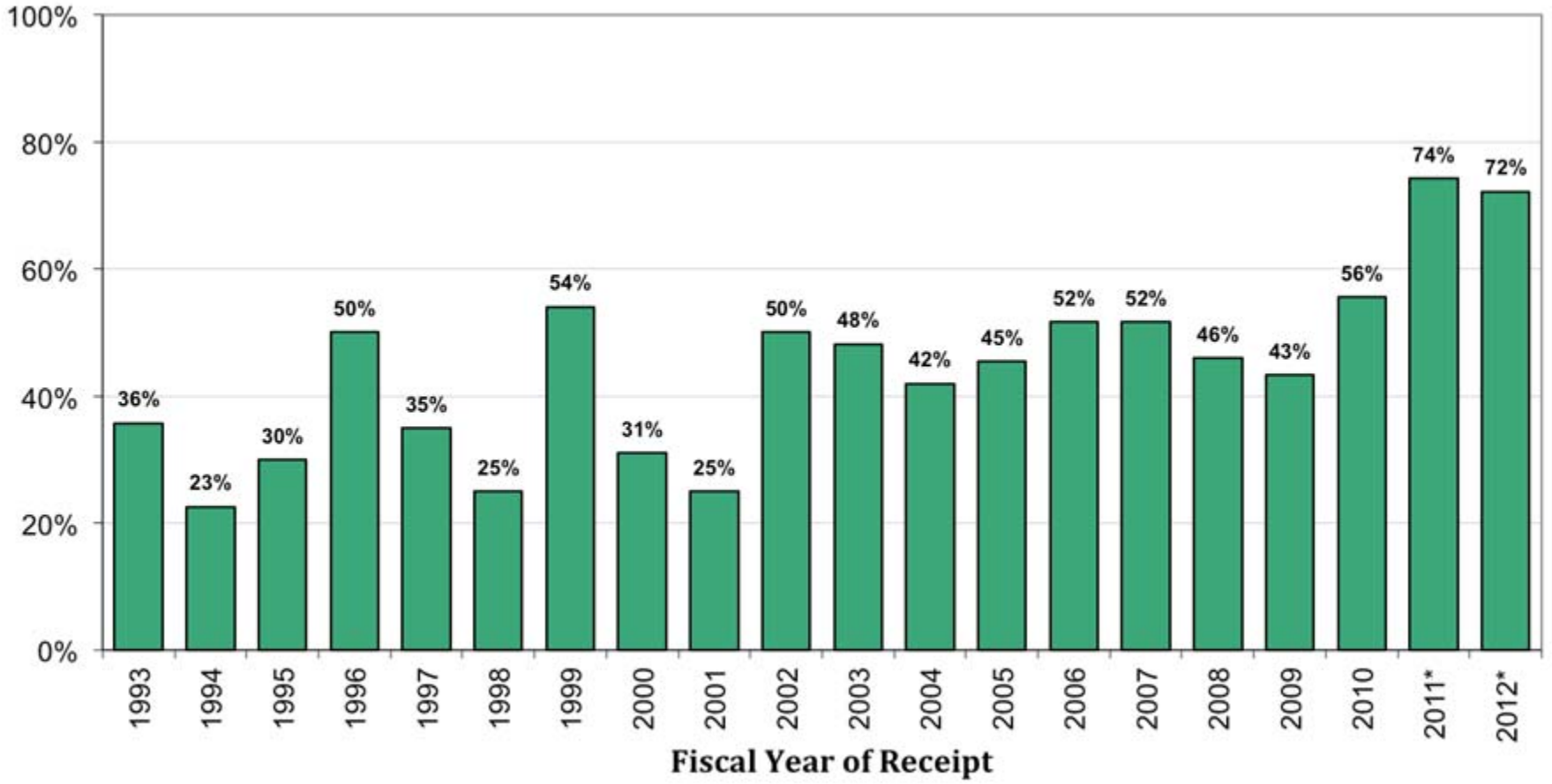
•*Data represents 12 month period of July 1st - June 30th

CDER New Molecular Entity and New Biologic Entity Filings and Approvals



- *CDER data as of 11/30/2012.
- *Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year.
- *Certain filed submissions are within their 60-day filing review period and may not be filed upon completion of the review.

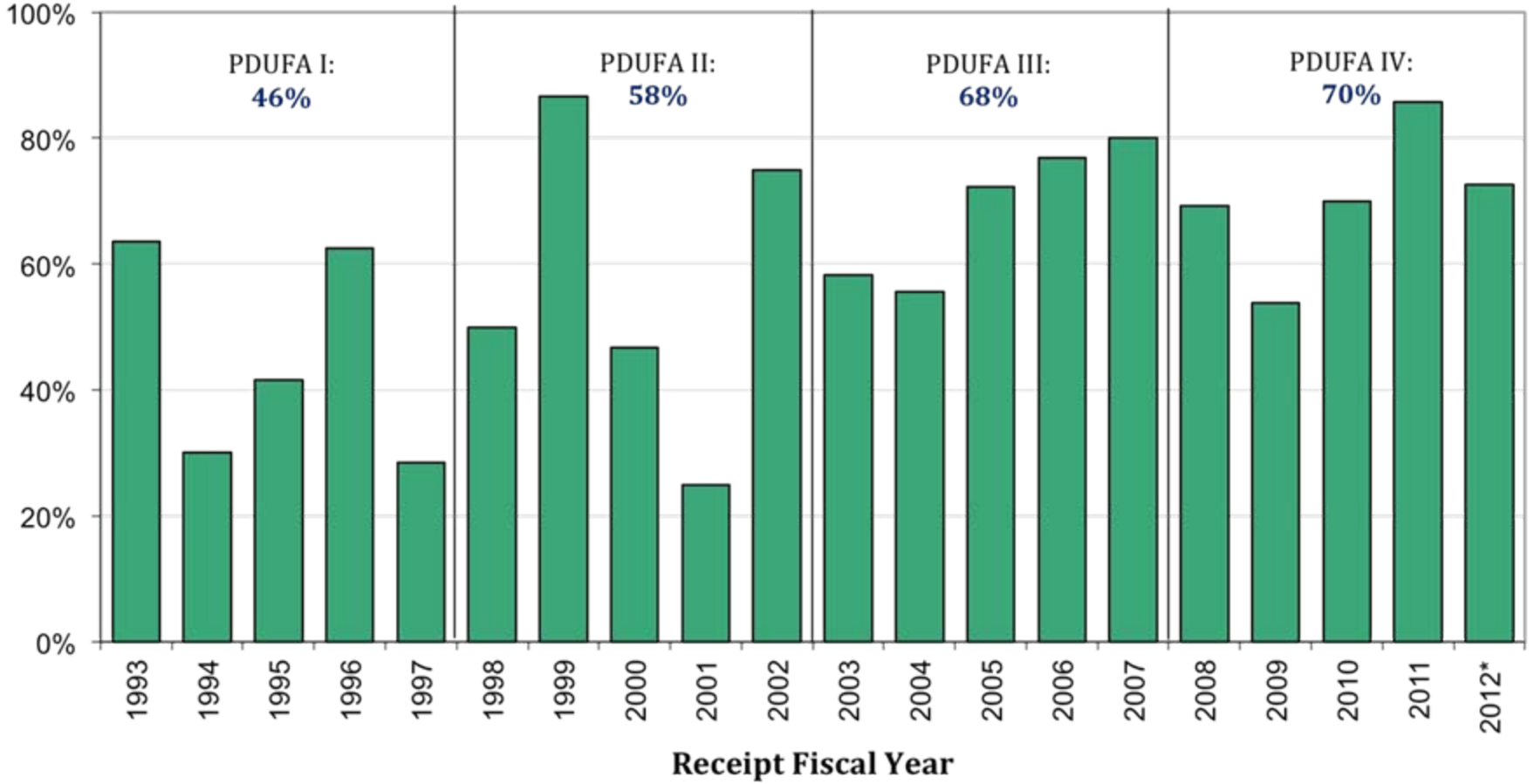
CDER NME/NBE First Action Approval Rate



•* FY'11 has one pending and FY'12 has twenty-five pending applications.

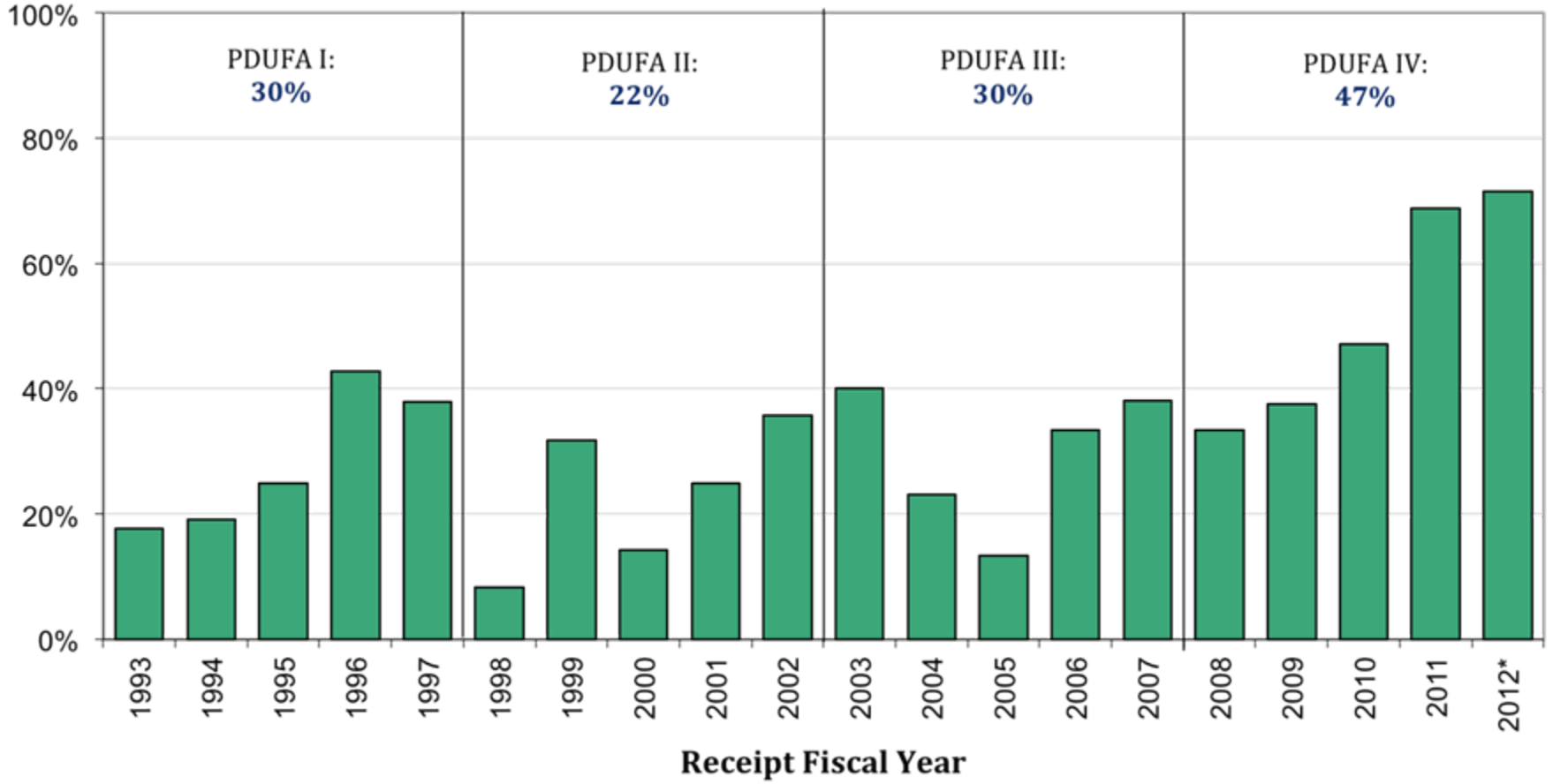
* CDER Data as of 11/30/2012 - FY 2011 and 2012 percentages exclude "Pending" from the denominator

CDER First Action Approval Rates for Priority NMEs/NBEs



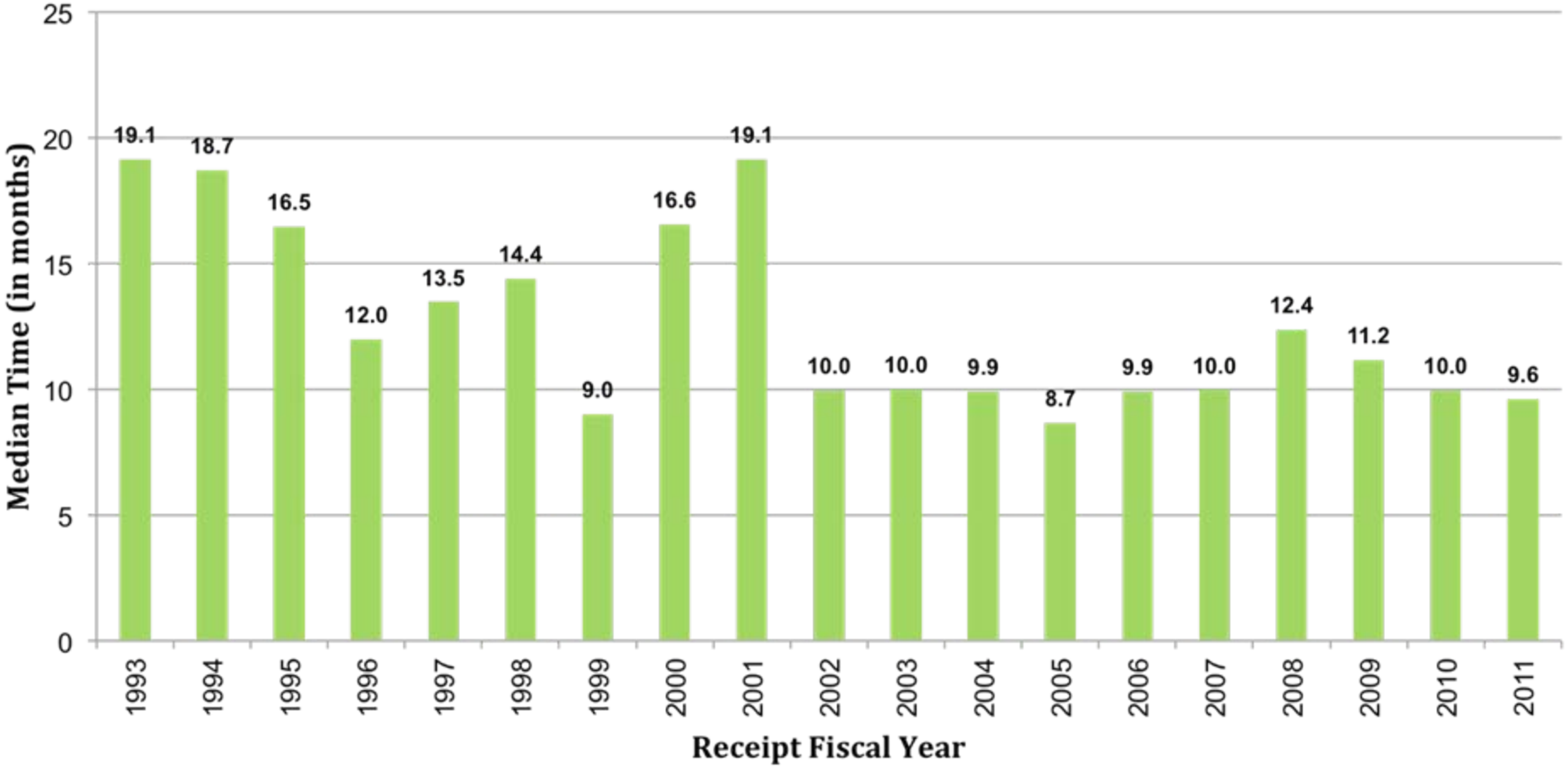
- FY '12 has five priority pending applications awaiting first action
- Potential for FY 2012 and PDUFA IV Priority FAAR to be 81% and 72% respectively
- NME and NBE actions data as of 11/30/2012.

CDER First Action Approval Rates for Standard NMEs/NBEs



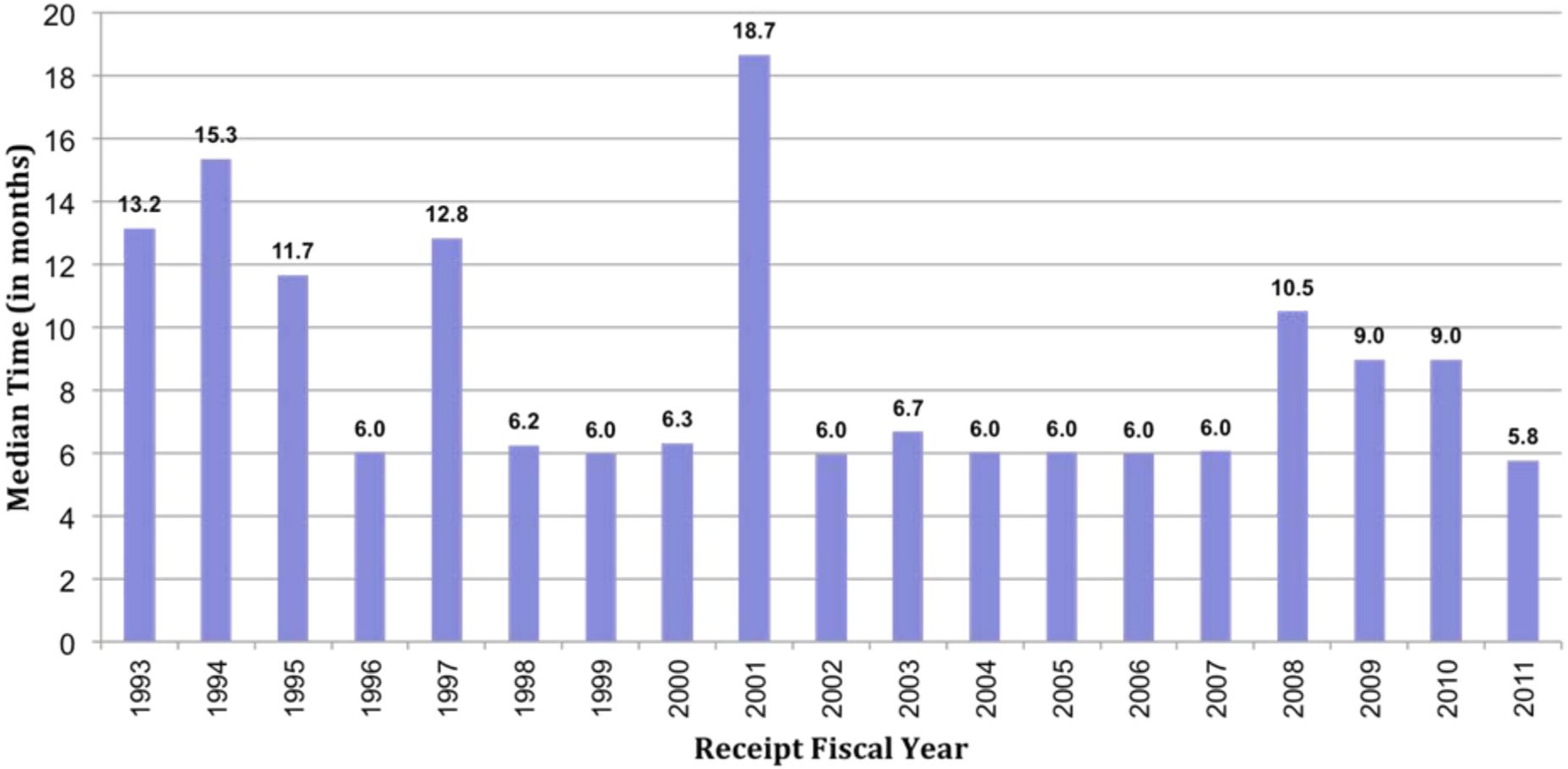
- * FY' 12 has twenty standard pending applications awaiting first action.
- NME and new BLA actions data as of 11/30/2012.

CDER Overall NMEs/NBEs Median Total Time to Approval



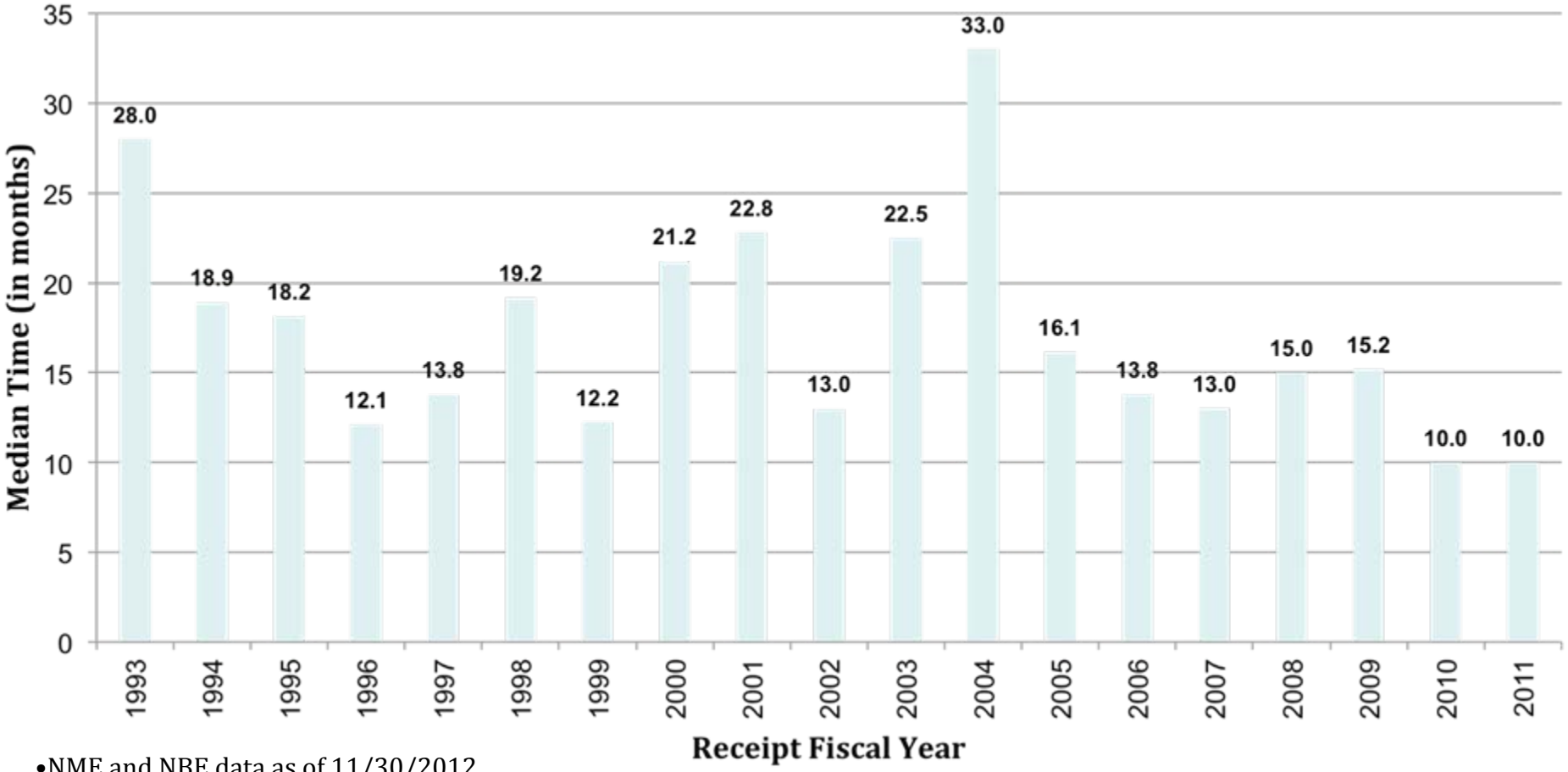
•NME and NBE data as of 11/30/2012.

CDER Priority NMEs/NBEs
Median Total Time to Approval



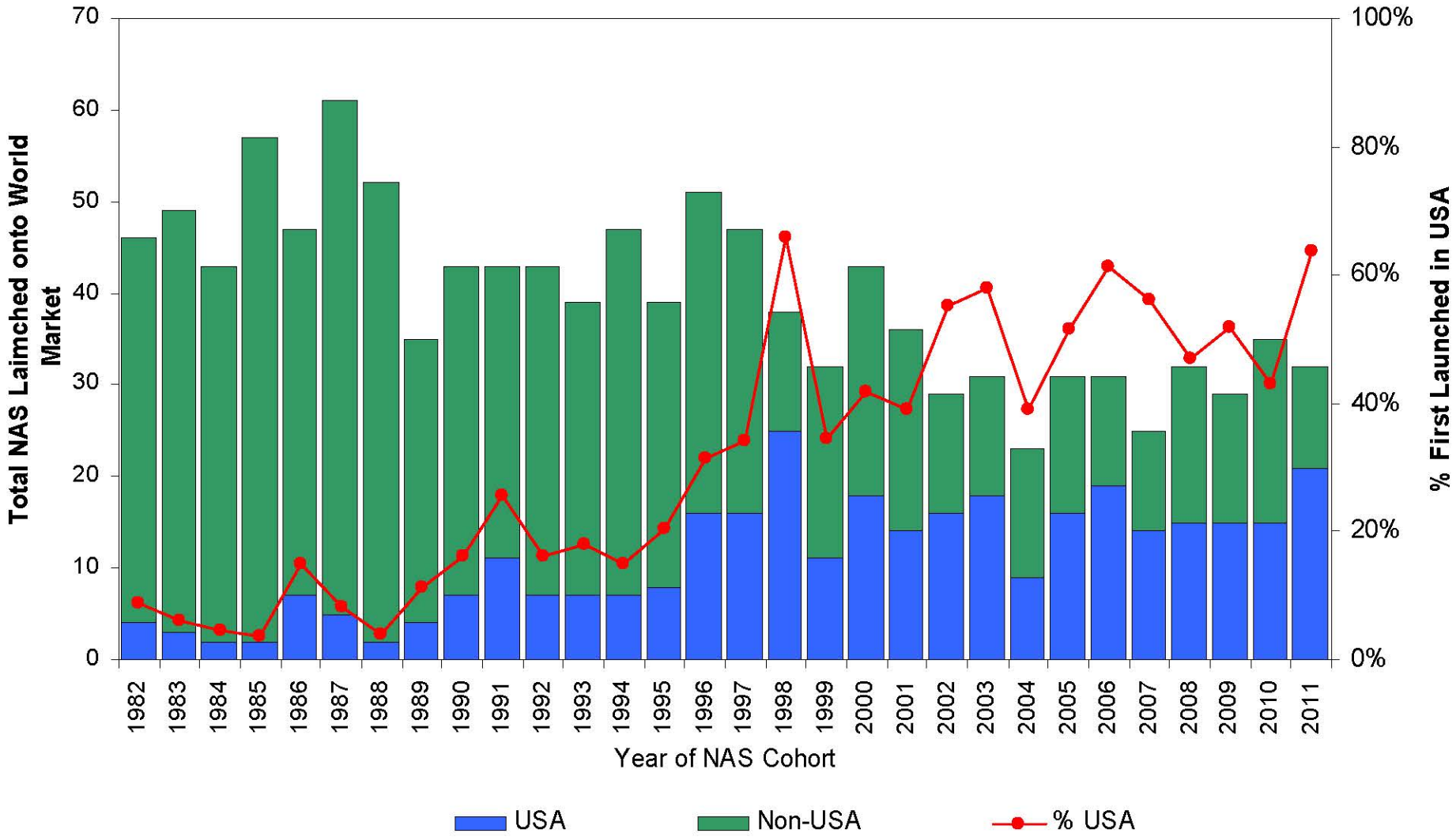
•NME and NBE data as of 11/30/2012.

CDER Standard NMEs/NBEs Median Total Time to Approval



•NME and NBE data as of 11/30/2012.

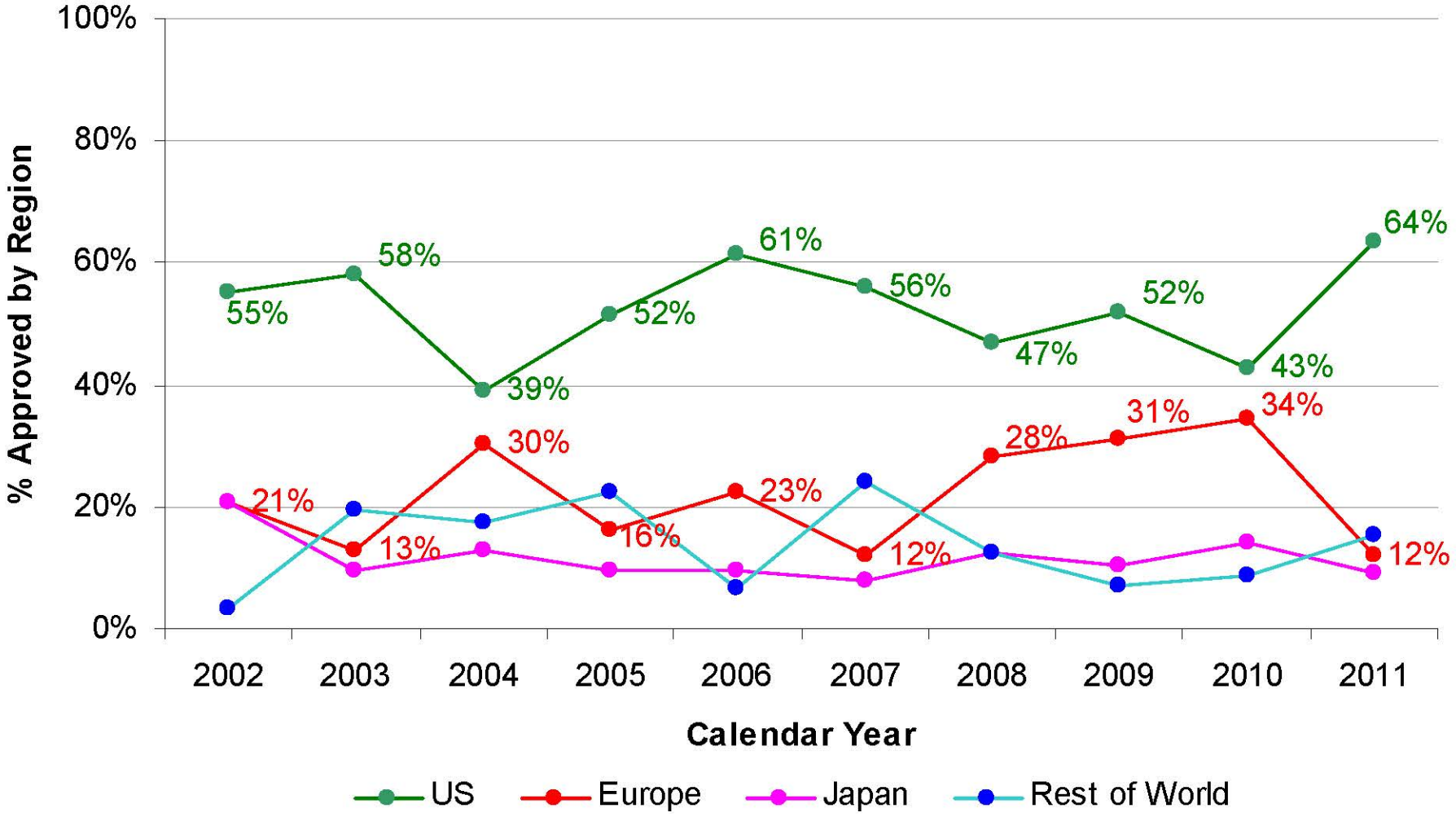
USA Share of New Active Substances First on World Market



Source: Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 - 2005), PharmaProjects/Citeline (2006 -2011) *www.citeline.com*

Global New Active Substance First Launches by Region

2002 - 2011



Source: Scrip Magazine (Feb 2003, Feb 2004, Feb 2005), Pharmaprojects (2006, 2007), Pharmaprojects R&D Annual Review (May 2008, May 2009, May 2010), Citeline Pharma R&D Annual Review (May 2011, May 2012)

www.citeline.com

Snapshot of CY 2012 NME Approvals* (1/2)

Trade Name	Met PDUFA Goal Date	Approved on First Cycle	Priority Approval	Fast Track	First-In-Class Drug	Approved First in the U.S.	Orphan Drug
VORAXAZE							
PICATO							
INLYTA							
ERIVEDGE							
KALYDECO							
ZIOPTAN							
SURFAXIN							
OMONTYS							
AMYVID							
STENDRA							
ELELYSO							
PERJETA							
BELVIQ							
MYRBETRIQ							

- *Data as of 11/30/12

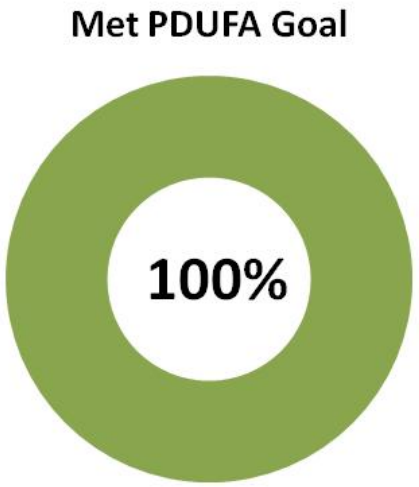
Snapshot of CY 2012 NME Approvals* (2/2)

Trade Name	Met PDUFA Goal Date	Approved on First Cycle	Priority Approval	Fast Track	First-In-Class Drug	Approved First in the U.S.	Orphan Drug
PREPOPIK							
KYPROLIS							
TUDORZA PRESSAIR							
ZALTRAP							
STRIBILD							
NEUTROVAL							
LINZESS							
XTANDI							
BOSULIF							
AUBAGIO							
CHOLINE C 11							
STIVARGA							
JETREA							
FYCOMPA							
SYNRIBO							
XELJANZ							
COMETRIQ							

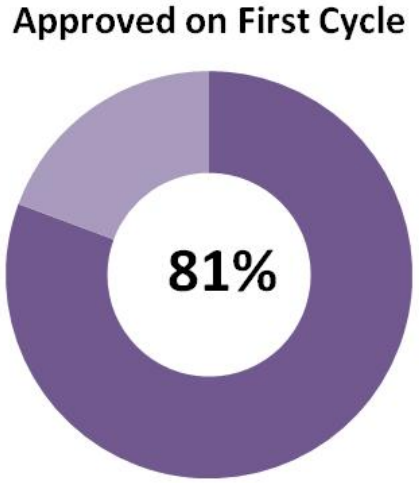
- *Data as of 11/30/12

In CY 2012, CDER continued to ensure the efficiency of first cycle review

- All NMEs approved to date in CY12 met their PDUFA goal dates

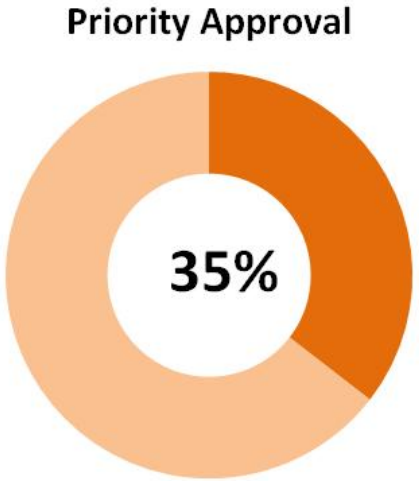


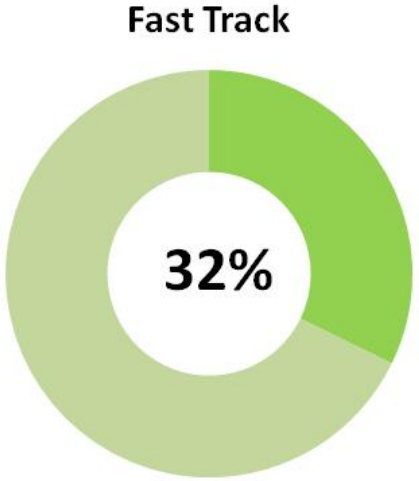
- 25 out of 31 (81%) NMEs approved to date in CY12 were approved in the first review cycle



CDER ensures that novel drugs receive expedited review

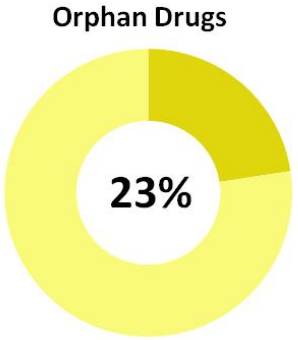
- 11 out of 31 (35%) NMEs approved to date in CY12 were approved under Priority Review
- 10 out of 31 (32%) NMEs approved to date in CY12 received Fast Track designation
- Kyprolis (Carfilzomib) and Synribo (Omacetaxine Mepesuccinate) were approved under the accelerated approval pathway



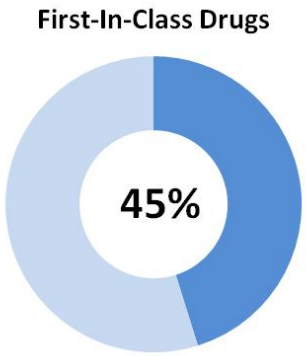


2012 was a strong year for drug innovation in the U.S.

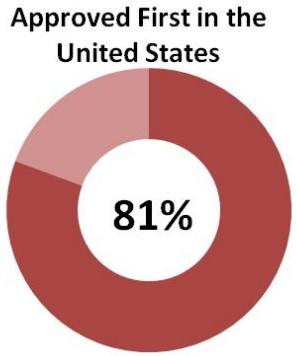
- Nearly one-quarter (23%) of NMEs approved to date in CY12 are for rare diseases



- Almost half (45%) of NMEs approved to date in CY12 are the first in their class



- Four out of five (81%) NMEs approved to date in CY12 were first approved in the U.S.



NME approvals for rare diseases CY 2006-2012

	NMEs and New Biologics	Rare (% of total approvals)
CY 2012*	31	7 (23%)
CY 2011	30	11(37%)
CY 2010	21	7 (33%)
CY 2009	26	9 (35%)
CY 2008	24	8 (33%)
CY 2007	18	6 (33%)
CY 2006	22	6 (29%)

- *Data as of Nov. 30, 2012
- Several NME applications for rare diseases have PDUFA goal dates before Dec 31, 2012.

CDER NME/NBE Rare Disease Drug Approval CY 2011-2012

- 2011, n=11 (12 indications)
  - Ipilimumab (melanoma)
  - Vandetinib (med. thyroid CA)
  - Belatacept (organ rejec, kdny tx, EBV+)
  - Brentuximab (Hodgkins)
  - Brentuximab (anapl. lge cell lymphoma)
  - Vemurafenib (melanoma BRAF+)
  - Crizotinib (NSCLC ALK+)
  - Icatibant (HAE)
  - Asparaginase (ALL)
  - Deferiprone (transfus. Fe overload due to thalassemias)
  - Clobazam (Lennox-Gastaut)
  - Ruxolitinib (Myelofibrosis)
- 2012, n = 7*
  - Glucarpidase (MTX toxicity)
  - Ivacaftor (Cystic Fibrosis)
  - Taliglucerase (Gaucher)
  - Carfilzomib(Multiple Myeloma)
  - Bosutinib (Chronic Myeloid Leukemia)
  - Omacetaxine Mepesuccinate (Chronic Myeloid Leukemia)
  - Cabozantinib(med. thyroid CA)

•* Data as of Nov. 30, 2012

Emerging role of emerging sponsors

- The new drug research and development paradigm is shifting rapidly from traditional big pharma to venture capital backed small companies
- Good news is that many small companies are successfully bringing innovative new products to market

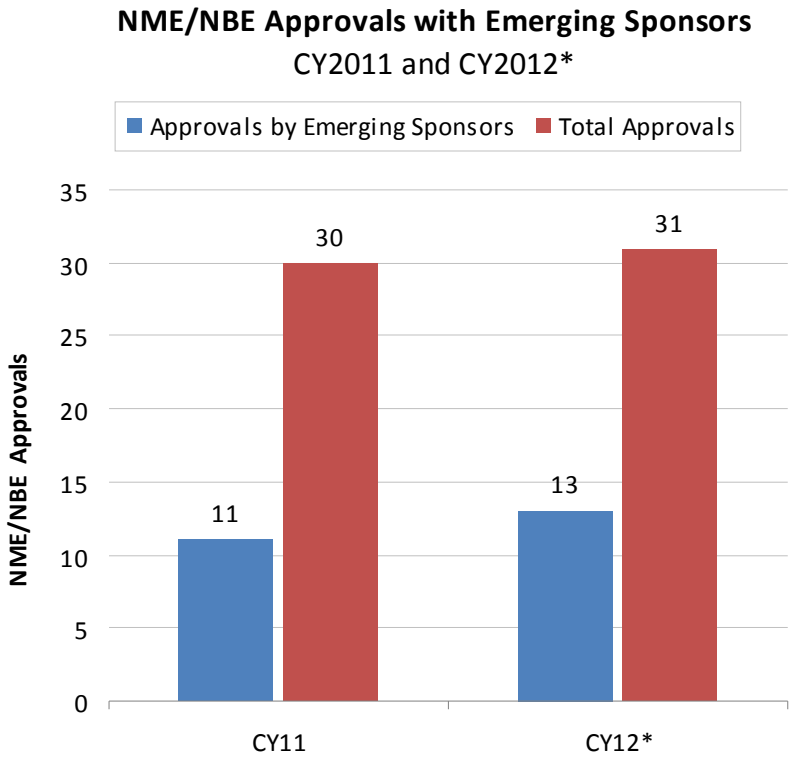
Emerging Sponsor Analysis: Analytical Approach

- Approvals categorized as those from "emerging" or "non-emerging" sponsors
  - An emerging sponsor is defined as the sponsor listed on the FDA approval letter who, at the time of approval, was not a holder of an approved application in the Orange Book or RMS/BLA
  - Sponsors are still classified as "emerging" even if they have partnership or parent relationships with sponsors currently with an approved product

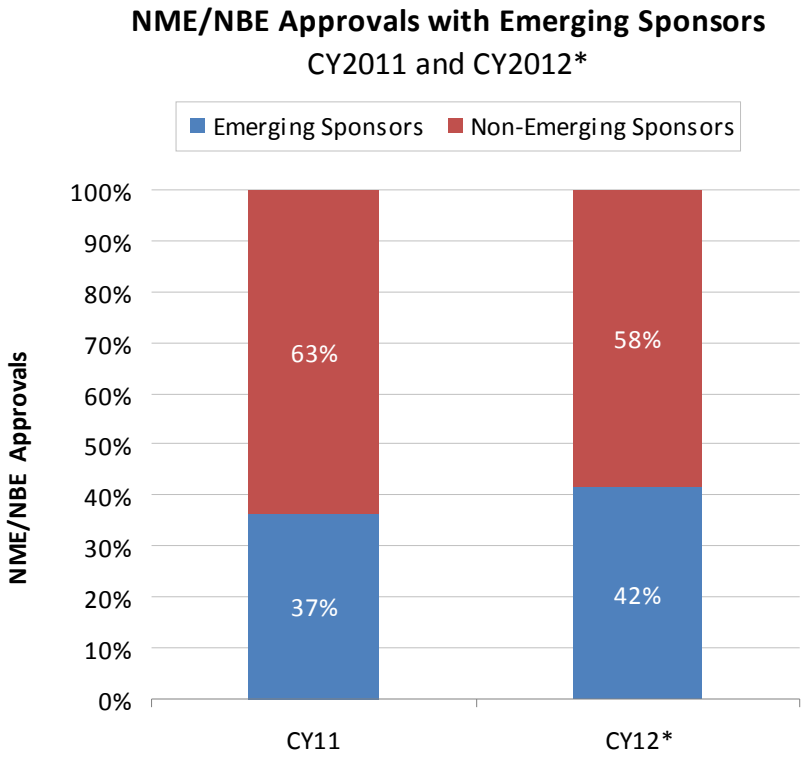
- Data sources include:
  - NME approval data from DARRTS
  - NBE approval data from RMS/BLA
  - Approved product data from FDA Orange Book
  - Parent company data from Dun & Bradstreet
  - Partnership data from sponsor websites

•Note: This approach involved some imputation of sponsor name since the same sponsor can appear in multiple forms in FDA data systems

Comparison of Emerging Sponsor Approvals: CY 2011-2012*



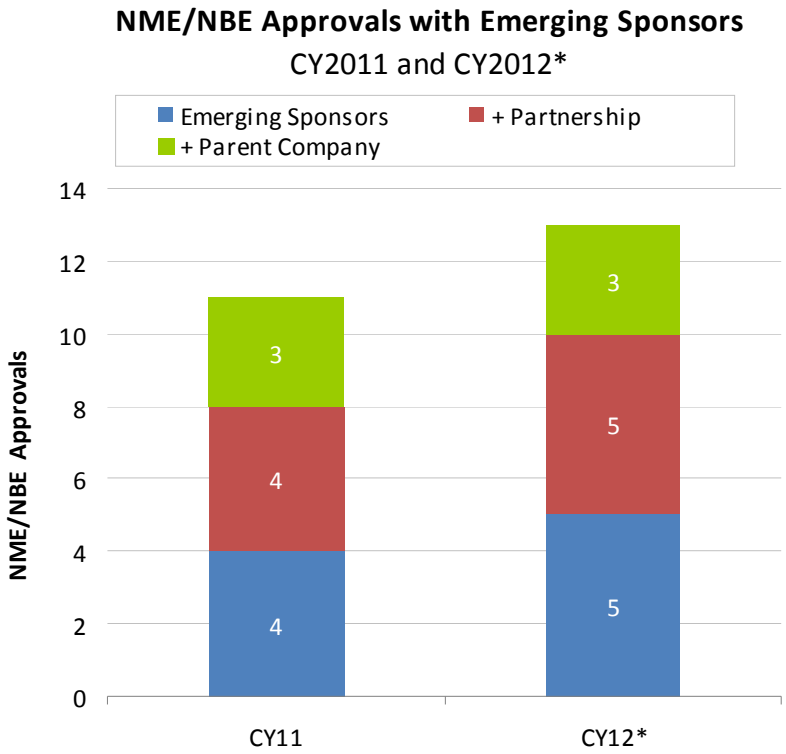
Source: FDA DBAR, Orange Book



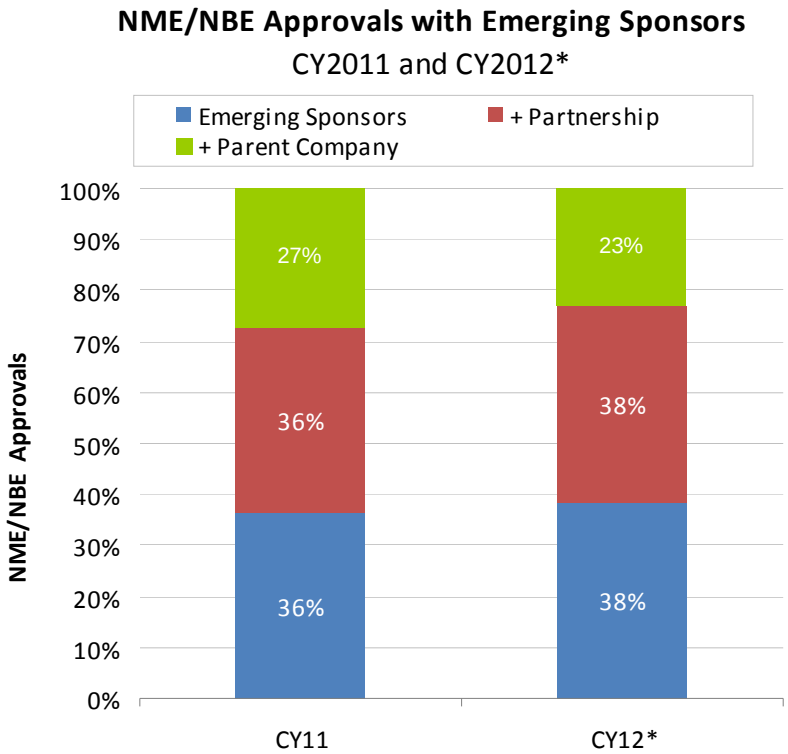
Source: FDA DBAR, Orange Book

- **2012 data as of December 3, 2012*

Comparison of Emerging Sponsor Approvals: Emerging Sponsors with Parent/Partnership Affiliation



Source: FDA DBAR, Orange Book



Source: FDA DBAR, Orange Book

- **2012 data as of December 3, 2012*

Emerging Sponsors for Calendar Year 2012*

	App Type	Trade Name	Applicant	Approval Date	Affiliation		
					None	Partner	Parent
1	NDA	Surfaxin	Discovery Laboratories Inc	6-Mar-12	✓		
2	NDA	Stendra	Vivus Inc	27-Apr-12	✓		
3	NDA	Choline C 11	Mayo Clinic Pet Radiochemistry Facility	12-Sep-12	✓		
4	BLA	Jetrea	Thrombogenics Inc.	17-Oct-12	✓		
5	NDA	Cometriq	Exelixis Inc	29-Nov-12	✓		
6	NDA	Omontys	Affymax Inc	27-Mar-12		✓	
7	NDA	Elelyso	Protalix Ltd	1-May-12		✓	
8	NDA	Belviq	Arena Pharmaceuticals Inc	27-Jun-12		✓	
9	NDA	Kyprolis	Onyx Pharmaceuticals Inc	20-Jul-12		✓	
10	NDA	Xtandi	Medivation Inc	31-Aug-12		✓	
11	NDA	Amyvid	Avid Radiopharmaceuticals Inc	6-Apr-12			✓
12	BLA	Neutroval	Sicor Biotech Uab	29-Aug-12			✓
13	NDA	Synribo	Ivax International Gmbh	26-Oct-12			✓

- **2012 data as of December 3, 2012*

Selected PDUFA V/FDASIA Programs That Impact Drug Development and Review

Review "Program" for NME NDAs and Original BLAs

Goal

- "Improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics." (PDUFA V Goals Letter)

Concept

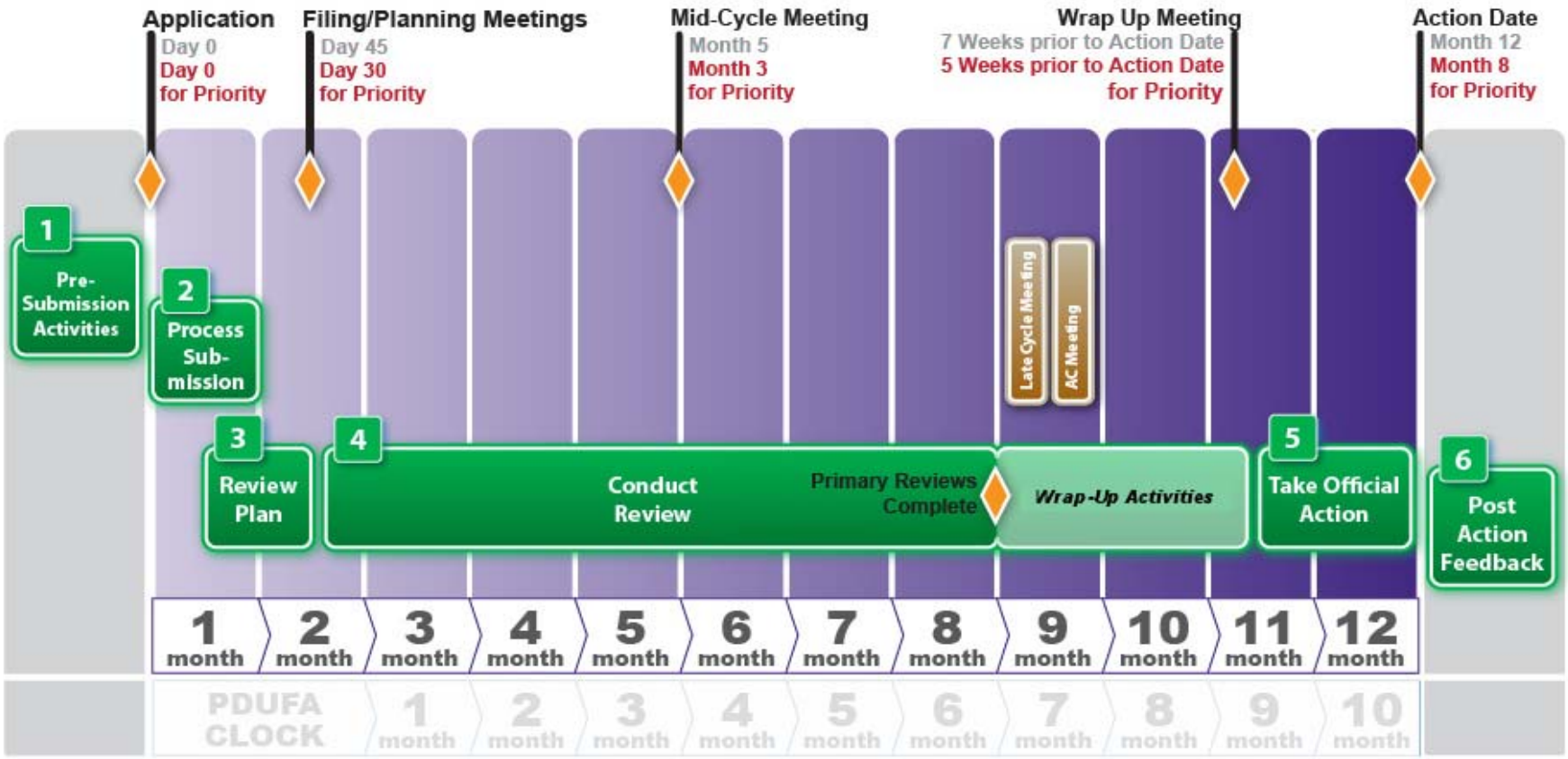
- Better planning before application submission, submission of complete applications, improved communication and transparency between applicant and review team during review, and additional review time will improve the efficiency of the first review cycle, which may decrease the number of additional review cycles prior to approval.

Review "Program" for NME NDAs and Original BLAs

Components

- Pre-submission meeting strongly encouraged
- Complete application at time of submission; incomplete subject to RTF
- 60-day filing review period "off the clock"
- 74-Day Letter
  - Planned review timeline, planned date of internal mid-cycle meeting, preliminary plans on need for AC meeting, early communication of deficiencies/information requests
- Mid-Cycle Communication
  - Within 2 weeks of internal mid-cycle meeting
  - Communication of significant issues identified to date/information requests, preliminary thinking on risk management/REMS, proposed dates for late-cycle meeting, updates on AC plans
- Discipline review letters
  - Summarize preliminary findings/deficiencies by discipline
- Late-cycle meeting (LCM)
  - Focus on information sharing, planning for AC, and planning for the remainder of review

Sample "Program" Review Timeline – Standard Application



Review "Program" Implementation

- Applies to all original NME applications and resubmissions following RTF received from 10/1/12 – 9/30/17
- 21st Century Desk Reference Guide (DRG) updated to include new activities and timelines for the Program
- Training for all staff involved in review of marketing applications completed
- Work ongoing to develop expectations, templates, ground rules for LCM
- Independent expert contractor hired to assess the program in real time
  - Interim report to be published for comment by March 31, 2015
  - Final report to be published for comment by December 31, 2016

Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

- **Goal**
  - Promote "timely interactive communication with sponsors during drug development…to help achieve the Agency's mission to facilitate the conduct of efficient and effective drug development programs…." (PDUFA V Goals Letter)
- **Components**
  - Dedicated liaison staff in OND to facilitate communication and to develop and deliver training on best practices to FDA staff and sponsors
  - Liaison staff serve as point of contact for general questions (e.g., which division to submit IND to) and secondary point of contact for sponsors encountering communications delays (e.g., >30 days) with review division
  - Provide training on best communication practices to CDER staff involved in IND review by end of FY14
  - Publish draft guidance on best communication practices by end of second quarter of FY15

Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development (2)

- **Implementation**
  - Acting team leader in place, work to establish and fill additional positions ongoing
  - Information posted to FDA website
    - http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm
  - Contact information for liaison team:
    - ONDEnhancedComm@fda.hhs.gov or 301-796-0319
  - To date:
    - 9 requests from external sources
    - Varied topics
      - Division assignment for IND, BLA review timeline, breakthrough therapy, IND exemption process, status of overdue CMC supplement, etc.

Breakthrough Therapies

- **FDASIA Section 902**
  - Created a "breakthrough therapy" designation designed to expedite the development and review of a drug when it is intended "to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."
  - A drug sponsor may request designation as a breakthrough therapy concurrently with, or any time after submission of an IND.

    Within 60 calendar days of receiving such a request, FDA must make a determination as to whether the drug qualifies as a breakthrough therapy.

Breakthrough Therapies (2)

- **FDASIA Section 902**
  - Actions to expedite development and review of a breakthrough therapy application may include:
    - holding meetings with the sponsor and the review team throughout the development of the drug;
    - providing timely advice to, and interactive communication with the sponsor regarding the development of the drug to ensure that the development program to gather the non-clinical and clinical data necessary for approval is as efficient as practicable;
    - involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review;
    - assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and
    - taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.

Breakthrough Therapies (3)

- **Implementation**
  - FDA is developing a draft guidance on expedited drug development and review pathways
    - Will articulate current thinking on Fast Track, Breakthrough, Priority Review, and Accelerated Approval
  - Information to guide BT submissions and OND contact information posted on FDA website
    - http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm
  - BT requests are reviewed by CDER's Medical Policy Council to ensure consistency in application of standards across divisions
  - CDER has received 7 BT designation requests to date
    - Two have been granted, one was denied, and 4 are pending within their goal dates

CDER New Drug Review: 2012 Summary

- CDER is meeting or exceeding nearly all PDUFA application review goals
- 31 NME approvals in 2012 is highest total since 2004; several more have PDUFA goal dates this year
- CDER has approved many important new drugs this year that will positively impact patients and public health
  - Approvals reflect broad use of existing mechanisms to expedite drug development and review
- NME first cycle approval rates for PDUFA IV at all time high
  - ≈50% first cycle approval rate for standard application still leaves room for improvement
  - Shift toward rare diseases and targeted therapy with favorable benefit/risk balance favors higher first-cycle approval rate

CDER New Drug Review: 2012 Summary (cont.)

- U.S. continues to lead the world in first approval of new active substances; U.S. patients benefit from early access
- Shift from big pharma to small company paradigm continues to change the dynamic of drug development and review
- We are "open for business" on new PDUFA V/FDASIA programs designed to expedite development of breakthrough therapies and enhance communication and efficiency during drug development and application review

Thank you!